

Claims

1. A process for the isolation and purification of HMG-CoA  
5 reductase inhibitors from a mycelium biomass which comprises:  
- clarifying a mycelium broth and concentrating the clarified  
broth to a lower volume,  
- acidifying of the concentrate to a pH value in the range of  
4.5 to 7.5, followed by extracting the HMG-CoA reductase  
10 inhibitor with ethyl acetate,  
- optionally performing lactonization,  
- crystallization of the HMG-CoA reductase inhibitor from a  
water-miscible or water-soluble organic solvent, and  
- crystallization of the HMG-CoA reductase inhibitor from an  
15 organic solvent having limited miscibility or solubility  
with water.

2. The process according to claim 1, further comprising,  
before clarifying the mycelium biomass broth, the steps of  
20 dissolving the HMG-CoA reductase inhibitor from a mycelium  
biomass at pH value between 9.5 and 13 into fermentation  
liquor, and adjusting the broth to a pH value between 7.5 and  
8.5.

25 3. The process according to claim 2, wherein the dissolution  
step is carried out at a temperature in the range of 10 to 40°C  
for less than one hour.

4. The process according to any one of the preceding claims,  
30 wherein clarifying the mycelium broth is carried out by  
removing the mycelium from the broth by means of filtration.

35 5. The process according to any one of the preceding claims,  
wherein said clarified broth is concentrated by means of  
reverse osmosis.

6. The process according to any one of the preceding claims, wherein the concentrate is acidified to a pH value in the range of 5.5 to 7.5.

5 7. The process according to claim 6, wherein the concentrate is acidified to a pH value in the range of 6.0 to 7.0.

8. The process according to any one of the preceding claims, wherein the HMG-CoA reductase inhibitor which is extracted  
10 from ethyl acetate and optionally lactonized is subjected to a purification step by adsorption chromatography.

9. The process according to claim 8, wherein a mixture of acetonitrile and water is used as the mobile phase for  
15 adsorption chromatography.

10. The process according to any one of the preceding claims, wherein the order of the crystallization steps is reversed.

20 11. The process according to any one of the preceding claims, wherein the water-miscible or water-soluble organic solvent used in the crystallization step is acetone or a low alkyl alcohol.

25 12. The process according to claim 11, wherein the crystallization step comprises dissolving the HMG-CoA reductase inhibitor in acetone, and then adding water thereto.

13. The process according to any one of the preceding claims,  
30 wherein the crystallization step from an organic solvent having limited miscibility or solubility with water comprises dissolving the HMG-CoA reductase inhibitor in said organic solvent at a concentration of 10 to 35 g/l, and removing one-third to three-fourth of said organic solvent.

35 14. The process according to any one of the preceding claims, wherein the organic solvent having limited miscibility or

solubility with water used in the crystallization step is ethyl acetate.

15. The process according to any one of the preceding claims,  
5 wherein HMG-CoA reductase inhibitors are obtained having a  
purity higher than 99.6%.

16. The process according to any one of the preceding claims,  
10 wherein the HMG-CoA reductase inhibitor is selected to be  
lovastatin.

17. A process for the purification of HMG-CoA reductase  
inhibitors which comprises subjecting the HMG-CoA  
reductase inhibitor to combined crystallization steps, which  
comprises crystallization from an water-miscible or water-  
soluble and crystallization from an organic solvent having  
limited miscibility or solubility with water, as final  
polishing steps to obtain HMG-CoA reductase inhibitors having a  
purity higher than 99.6%.

18. The process according to claim 17, wherein the obtained  
HMG-CoA reductase inhibitors have purity higher than 99.7 %.

19. The process according to claim 1 or 18, wherein wherein  
acetone or a low alkyl alcohol is used as the water-miscible or  
water-soluble organic solvent.

20. The process according to claim 19, wherein said  
crystallization comprises dissolving the HMG-CoA reductase  
inhibitor in acetone and then adding water thereto.

21. The process according to any one of claims 17 to 20,  
wherein said crystallization from said organic solvent having  
limited miscibility or solubility with water comprises  
35 dissolving the HMG-CoA reductase inhibitor in said organic  
solvent at a concentration of 10 to 35 g/l, and removing one-  
third to three-fourth of said organic solvent.

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22. The process according to any one of claims 17 to 21,  
wherein ethyl acetate is used as the organic solvent having  
limited miscibility or solubility with water.

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23. Use of a process according to claim 1 or a process  
according to claim 17 for the isolation and/or purification of  
lovastatin.

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